Draft Guidance for Industry
Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products
Chemistry, Manufacturing, and Controls Documentation

Docket No. 99D-1454, CDER 98185, June 2 , 1999
Page 29657 [FR Doc. 99-13921]

Lines 862 - 863 - DIMENSIONAL MEASUREMENTS
Acceptance criteria, test procedures, and analytical sampling plans
• Physicochemical parameters and dimensional measurements of the 862 container, closure, and pump components 863

The above statement can be misleading - the pharmaceutical company may interpret this as disassembling the nasal spray pump and measuring the individual pump component dimensions - the dimensions of the *disassembled* components are likely to differ from the dimensions of those components prior to assembly.

The nasal spray pump supplier should measure individual pump component dimensions as routine in-process controls, and provide assurance to the pharmaceutical company that all dimensions are within the established specifications. It would be more appropriate for the pharmaceutical company to measure the dimensions on the ***assembled*** pump, as well as carry out functionality tests, as incoming quality control.

99D-1454

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Comments by Valois SA - Nasal Spray Pump/Packaging Supplier

August 27th, 1999

of all section were summed. Counts of the individual sections divided by the total count results in the deposition fraction within the section.

Results

Duplicate exposures were performed for each of the four nozzle types (VP-7, PF-35, PF-60, and PF-80). Deposition data from each major east section (anterior, middle, and posterior) along with the filter sample were averaged across the duplicate runs and plotted for each nozzle type. Figure 2 is a graphical representation of the percent deposition in each major cast region and filter sample for each of the four nozzle types.

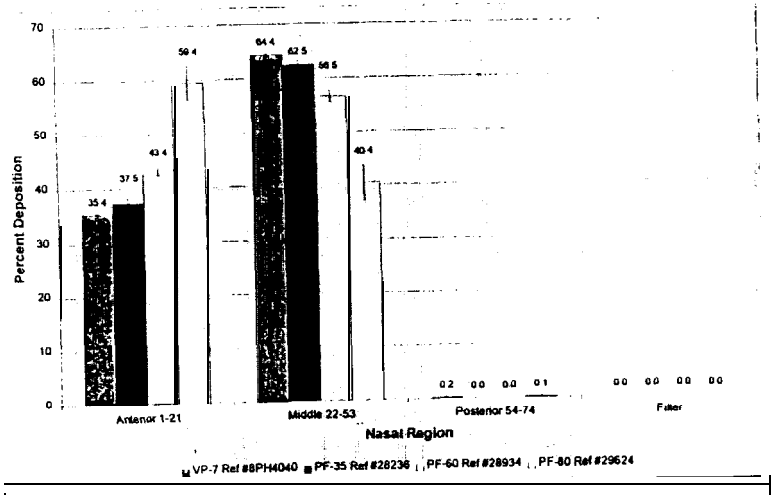

Figure 2. Deposition pattern in **the anterior, turbinate, and posterior regions of the** nasal airway

Our data showed that the test material was mainty deposited in the anterior and turhinate regions with little passing beyond the nasopharyngeal region. Over 99.98% of the test material deposited in the nose. This result is similar to data obtained in human volunteers (Newman et al., 1987; Suman et al, 1998), indicating that our technique of using the nasal cast can be considered as an equivalent mefhod by which to determine deposition patterns.

More detailed deposition information can be shown in the turbinate region where the deposition patterns in the superior middle and inferior meatus regions were mapped as a function of distance. These data showed that in most cases deposition was high toward the anterior portion of the turbinate region where most deposition was concentrated in the inferior meatus. There were: however, deposition spots at the middle and posterior portions of the turbinate region, This showed a non-uniform deposition pattern in the tuibinatc area, which may well hc correlated with the flow pattern in the nasal airway.

Although deposition patterns for the four different spray pumps were similar qualitatively; they were different quantitatively. Deposition patterns for VP-7 and PF-35 were similar with 35.4 and 37.5% deposition in the anterior region, and 64.4% and 62.5% in the turbinate regions, respectively. The deposition pattern for PF-60 was probably less favorable with 59.4% in the anterior region. The deposition pattern for PF-80 was better with 43.4% and 56.5% in the anterior and turbinate regions, respectively. Based on this comparison, VP-7 and PF-35 would be recommended because they produced droplets that deposited more in the turbinate area.

Conclusions

The deposition measurement obtained in the human nasal airways showed detailed local deposition pattrms with reproducible results. It provided quantitative data on where much of the test material was &posited. Our data showed that the test material was mainly deposited in the anterior and turbinate regions with little passing beyond the nasopharyngeal region.

References

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DEPOSITION PATTERN OF A NASAL SPRAYIN THE HUMAN NASAL AIRWAY

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Summary

This paper describes deposition patterns of an anti-virus compound generated from four designs of nasal sprays using a multi-sectional nasal airway model. An human nasal replica made from *in vivo* MRI scan of an adult male human consists of 74, 1.5 mm-thick, acrylic plastic sections was used. Our data showed that the material was mainly deposited in the anterior and turbinate regions with little passing beyond the nasopharyngeal region. Detailed deposition information was shown in the turbinate region, indicating that deposition was high toward the anterior portion region where most deposition was concentrated in the inferior meatus. There were, however, deposition spots at the middle and posterior portions of the turbinate region, This non-uniform deposition pattern in the turbinate area may be correlated with the flow pattern.

Introduction

The nasal airways are one entry to the respiratory tract. The nasal airways act like a filtration system or first defense to remove particles before entering the lung. A high percentage of very large (> S pm) and very small particles (<0.01 pm) is retained in the nasal passages (Cheng et al., 1991). Nasal sprays, liquid droppers, nebulizers, and pressurized meter dose inhalers (pMDIs) are used to deliver drugs into the nose (Hardy et al., 1985; Newman et al., 1987; Harris et al,, 1988; Jager-Waldau, 1992). 'Distribution of drugs in the nasal airway depends on the droplet size and velocity of the droplets. Spray pumps that *produce* panicles > IO µm deposit drugs in the anterior portion of the nose, and a significant area of the nasal cavity is thus unexposed to the drug (Hardy et al.,1985; Suman et al., 1998). Droplets generated from pMDIs also deposit primarily in the anterior area of the nose presumably because of the high initial velocity of the droplets (Newman et al., 1987). On the other hand, droplets generated from liquid droppers and nebulizers deposit more uniformly in the nose (Hardy et al., 1985; Suman et al., 1998). These deposition studies were. performed in human volunteers. Nasal airway replicas made from cadavers or from magnetic resonance images (MRIs) of human volunteers (Cheng et al., 1993; Guilmette et al., 1994) have been used IO study mechanisms of particle deposition in the human nasal airway. Nasal deposition efficiency obtained in airway casts agrees well with data obtamed in human volunteers (Cheng et al., 1996). local deposition patterns can also be obtained by using a multi-sectional nasal airway model made from MRI scans (Chcng et al., 1993; Guilmette and Gagliano, 1994).

The purpose of this study was to determine the deposition patterns of an anti-virus compound generated from four different designs of nasal spray pumps using a multi-sectional nasal airway model made from MRI scans. Results of this study will help to determine an optimal design for the spray pump.

Material and Methods

An human nasal replica made from in vivo MRI scan of an adult male human consists of 74, I.5 mm-thick, acrylic plastic sections was used for the study. This replica encompasses the airways from the anterior nares to the posterior nasopharynx. A digital photograph of the nasal cast is shown in Figure I. The exit of the nasal replica was connected to a filter sampler and to a flow meter IO control the inspiratory flow rate for the experiment. A constant inspiratory flow of 20 L min^{-1} was maintained during the exposure portion of this study. The flow rate was calibrated used a digital flow meter (Model 821-S1-M3, Sierra Instruments Inc., Monterey, CA). The model was checked for leak before every test. The pump sprays were loaded with H-labeled compound, and two shots of nasal spray were applied into the right nostril. The model was held in this position for I minute at which time the flow to the model was turned off. Duplicate samples were made for each spray.

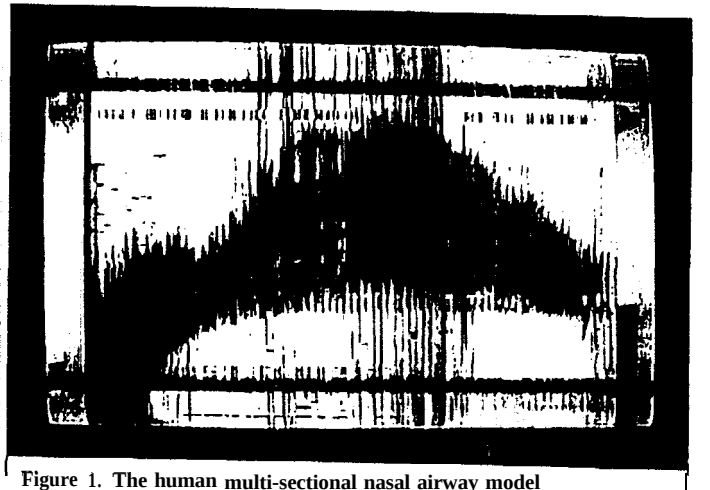

Figure 1. The human multi-sectional nasal airway model

After approximately 15 minutes of exposure, the model was disassembled with care taken to maintain proper orientation of the airway. The anterior and posterior sections of the cast were removed and washed as two complete subassemblies. The middle turbinate region of the cast was separated into individual components, and one third, IO plates, of this section were washed carefully (the superior, middle, and inferior meatii were washed separately within each plate). The remaining IWO thirds of the middle section was washed as a complete subassembly. The wash was collected in separate containers. From all samples, 0.5 ml of each wash was removed from the container in which that section was washed and placed into a 20 ml scintillation vial for counting. Scintillation cocktail (15 ml) was added to each sample. The samples were counted using a Packard Liquid Scintillation Analyzer (Model, Tri Carb 2500TR, Packard Instrument Company, Meriden, CT 06450). The total net counts

DDTL, 1998.